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EXAMINER	
POPA, ILEANA	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/045,178	KASAHARA ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-46,49-51,56,58,59,61,63-73,75 and 77-82* is/are pending in the application.

4a) Of the above claim(s) *46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-45,49-51,56,58,59,61,63-73,75 and 77-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' submission of amended list of claims on 09/09/2005 is acknowledged. Claims 41, 66, and 80-82 have been amended to recite that the claimed methods include a step of contacting the subject with a prodrug that is activated by the expression of the suicide gene. Since the specification supports the amendments (p. 71, lines 22-26 and p. 73, lines20-25), no new matter has been introduced.

Claims 1-40, 47, 48, 52-55, 57, 60, 62, 74, and 76 have been cancelled. Claim 46 has been withdrawn.

Claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, and 77-82 are pending.

Note: Change in Examiner, Art Unit and SPE

The examiner on record is Ileana Popa, Art Unit 1633. Therefore, future correspondence should reflect such changes. The information regarding the SPE and Art Unit is at the end of the Action.

Double Patenting

2. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In

re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Claims 41-45, 49-51, 56, 58, 59, 61, 63-65, 80 and 81 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 20 of U.S. Patent No. 6,899, 871. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claim 41 is drawn to a method of treating a subject having a proliferative disorder comprising: contacting the subject with (i) a therapeutically effective amount of a retrovirus comprising a retroviral GAG protein, a retroviral POL protein, a retroviral envelope that could be a chimeric protein that comprises an env protein and a targeting polypeptide, an oncoretroviral polynucleotide sequence comprising LTR sequences at the 5' and 3' end of the retroviral genome, wherein a tissue-specific promoter sequence is contained within the LTR sequence at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid sequence encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell,

on a pharmaceutically acceptable carrier, and (ii) a prodrug that is activated by the expression of the suicide gene (claims 1, 63, and 64). The subject is a mammal, wherein the mammal is a human (claims 42 and 43), administration is systemic, local or topical (claim 45), the oncoretroviral polynucleotide sequence is selected from a group consisting of MLV, MoMLV, GALV, and HFV (claim 49), the MLV is an amphotropic MLV (claim 50), the env protein is selected from a group consisting of MLV env and VSV env (claim 51), the cell proliferative disorder is selected from a group consisting of lung cancer, colon-rectum cancer, breast cancer, prostate cancer, urinary tract cancer, uterine cancer, lymphoma, oral cancer, pancreatic cancer, leukemia, melanoma, stomach cancer and ovarian cancer (claim 56), the tissue specific promoter is associated with a growth regulatory gene (claim 58) wherein the growth regulatory gene is probasin (claim 59), the suicide gene is thymidine kinase or a purine nucleoside phosphorylase (claim 61), the targeting polypeptide is an antibody, a receptor, or a receptor ligand (claim 65).

The instant claim 80 is drawn to method of treating a subject having a cell proliferation disorder comprising: contacting the subject with (i) a therapeutically effective amount of a recombinant replication competent MLV comprising an MLV GAG protein, an MLV POL protein, an MLV polynucleotide sequence comprising LTR sequences at the 5' and 3' end of the MLV polynucleotide sequence, wherein a target-specific promoter sequence is contained within the LTR sequence at the 5' or 3' or 5' and 3' end of the MLV polynucleotide sequence, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic

acid sequence encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell, on a pharmaceutically acceptable carrier, and (ii) a prodrug that is activated by the expression of the suicide gene.

The instant claim claim 81 is drawn to a method of treating a subject having a proliferative disorder comprising contacting the subject with (i) a therapeutically effective amount of a recombinant replication competent retrovirus comprising a retroviral GAG protein, a retroviral POL protein, a retroviral envelope comprising a chimeric env protein comprising a targeting ligand, an oncoretroviral polynucleotide sequence comprising LTR sequences at the 5' and 3' end of the oncoretroviral polynucleotide sequence, wherein a tissue-specific promoter sequence is contained within the U3 region of the LTR sequences at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid sequence encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell, and (ii) a prodrug that is activated by the expression of the suicide gene.

The patented claim 20 recites a method of treating a subject having a cell proliferation disorder comprising: contacting the subject with (i) a therapeutically effective amount of a replication competent retrovirus comprising a retroviral GAG protein, a retroviral POL protein, a retroviral envelope, an oncoretroviral polynucleotide sequence comprising LTR sequences at the 5' or 3' or 5' and 3' end of the

oncoretroviral polynucleotide sequence, a cassette comprising an IRES operably linked to a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug, wherein the cassette is positioned 5' to the 3' LTR sequence and/or 3' to the sequence encoding the retroviral envelope, and cis-acting sequences for reverse transcription, packaging and integration in a target cell, and (ii) a nontoxic prodrug that is converted into a toxic drug by the polypeptide.

The instant retrovirus and the patented replication competent retrovirus are identical, as exemplified by Fig. 2A of the instant application and Fig. 2A of the patent that both disclose a replication competent retrovirus comprising a cassette with an IRES operably linked to a nucleic acid sequence encoding a suicide gene. With respect to the limitation recited in the instant claims 42-45, 49-51, 58, 59, 61, 63-65, and to the limitation of chimeric env recited in claim 81, the specification discloses that the subject can be any mammal, preferably a human and contacting is *in vivo* by systemic, topical or directly to the site, i.e., local administration (column 18, lines 45-56), the env protein could be MLV or VSV env (column 13, lines 10-20), the cell proliferative disease could be lung cancer, colon-rectum cancer, breast cancer, prostate cancer, urinary tract cancer, uterine cancer, lymphoma, oral cancer, pancreatic cancer, leukemia, melanoma, stomach cancer and ovarian cancer, the tissue-specific promoter is associated with a growth regulatory sequence, such as probasin (column 2, lines 50-55), the heterologous nucleic acid sequence that converts a nontoxic prodrug to a toxic drug, i.e., a suicide gene, could be thymidine kinase or PNP (column 9, lines 35 and 36), the retroviral env could be chimeric, comprising a targeting polypeptide, wherein

the targeting polypeptide is an antibody, a receptor or a receptor ligand (column 12, lines 9-16). With respect to the limitation of the oncoretroviral polynucleotide sequence being MLV (wherein MLV is an amphotropic MLV), GALV, and HFV, the genus of oncoretroviral polynucleotide recited in the patent claim 20 encompasses these species. With respect to the limitation of a recombinant replication competent MLV, as recited in the instant claim 80, the genus of a replication competent retrovirus, as recited in the patented claim 20, anticipates this species.

Thus, the patented claim 20 anticipates claims 41-45, 49-51, 56, 58, 59, 61, 63-65 and 80 of the instant application. Since claim 20 of the US Patent No. 6,899, 871 embraces all limitation of the instant claims, the patent claim and the application claims are obvious variants of one another.

Claims 66-73, 75, 77-79 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 and 21 of U.S. Patent No. 6,899, 871. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims claims 66-68 are drawn to a method of treating a subject having a proliferative disorder comprising: contacting the subject with (i) a therapeutically effective amount of a retroviral polynucleotide comprising a polynucleotide sequence encoding a GAG protein, a polynucleotide sequence encoding a POL protein, a polynucleotide sequence encoding a retroviral envelope that could be a chimeric protein that comprises an env protein and a targeting polypeptide, an

oncoretroviral polynucleotide sequence comprising a LTR at the 5' and 3' end of the oncoretroviral polynucleotide sequence, wherein a target-specific promoter sequence is contained within the U3 region of the LTR sequence at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence, a heterologous polynucleotide sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid sequence encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell, and (ii) a prodrug that is activated by the expression of the suicide gene. The env protein is selected from a group consisting of MLV env and VSV env (claim 73), the suicide gene is thymidine kinase or a purine nucleoside phosphorylase (claim 75), the targeting polypeptide is an antibody, a receptor, or a receptor ligand (claim 69), GAG, POL, and retroviral envelope polynucleotide sequences are from MLV or MoMLV (claim 70), wherein the MoMLV is an amphotropic MoMLV, env protein is an ecotropic protein (claim 72), the regulatory nucleic acid sequence operably linked with the heterologous nucleic acid sequence is selected from the group consisting of a promoter, enhancer, and an IRES (claim 77), the polynucleotide sequence is contained in a viral particle (claim 78) or in a pharmaceutically acceptable carrier (claim 79).

The patented claim 1 recites a method of treating a subject having a cell proliferation disorder comprising: contacting the subject with a (i) therapeutically effective amount of a replication competent retrovirus comprising a nucleic acid sequence encoding a retroviral GAG protein, a nucleic acid sequence encoding a POL protein, a nucleic acid sequence encoding a retroviral envelope, an oncoretroviral

polynucleotide sequence comprising LTR sequences at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence, a cassette comprising an IRES operably linked to a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug, wherein the cassette is postioned 5' to the 3'LTR sequence and/or 3' to the sequence encoding the retroviral envelope, and cis-acting sequences for reverse transcription, packaging and integration into the genome, and (ii) a nontoxic prodrug that is converted to a toxic drug by the polypeptide. The proliferative disorder is selected from a group consisting of various types of cancer (claims 2 and 10), the LTR further comprises a tissue-specific promoter (claim 3), wherein the tissue-specific promoter comprises at least one ARE (claim 11), the nucleotides –426 to +28 of the rat probasin gene (claim 12), the ARE is obtained from probasin gene (claim 13), the suicide gene is thymidine kinase or PNP (claim 4), the retroviral env is chimeric and comprises a targeting ligand (claim 5), wherein the targeting ligand is an antibody, a receptor, or a receptor ligand (claim 14), the subject is a mammal, wherein the mammal is a human (claims 6 and 15), the administration of the retrovirus is *in vivo* (claim 7), wherein the *in vivo* administration is systemic, local or topical (claim 16), the oncoviral polynucleotide sequence is selected from MLV, MoMLV, GALV and HFV (claim 8), wherein MLV is an amphotropic MLV (claim 17), and the retrovirus is contained in a pharmaceutically acceptable carrier (claim 9).

The patented claim 18 recites a method of treating a subject having a cell proliferation disorder comprising: contacting the subject with a (i) therapeutically effective amount of a replication competent retrovirus comprising a nucleic acid

sequence encoding a retroviral GAG protein, a nucleic acid sequence encoding a POL protein, a nucleic acid sequence encoding a retroviral envelope (claim 18), an oncoretroviral polynucleotide sequence comprising LTR sequences at the 5' and 3' of the retroviral genome, wherein a tissue-specific promoter sequenced is contained within the LTR sequences at the 5' or 3' or 5'and 3'end of the oncoretroviral polynucleotide sequence, wherein the tissue-specific promoter sequence comprises at least one ARE obtained from the probasin promoter, a cassette comprising an IRES operably linked to a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug, wherein the cassette is postioned 3' to the sequence encoding the retroviral envelope and 5' to the 3'LTR sequence and/or 3' to the sequence encoding the retroviral envelope, and cis-acting sequences for reverse transcription, packaging and integration into the genome, and (ii) a nontoxic prodrug that is converted to a toxic drug by the polypeptide.

The patented claim 21 recites a method of treating a subject having a cell proliferation disorder comprising: contacting the subject with a (i) therapeutically effective amount of a replication competent retrovirus comprising an oncoretroviral polynucleotide sequences comprising cis-acting sequences for reverse transcription, packaging and integration and LTR sequences at the 5' and/or 3' end of the oncoretroviral polynucleotide sequence, a cassette comprising an IRES operably linked to a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug, wherein the cassette is positioned 5' to the 3'LTR sequence and/or 3' to the sequence encoding the retroviral envelope, and (ii) a nontoxic

prodrug that is converted to a toxic drug by the polypeptide.

Basically, the patented claims 1, 18, and 21 recite the same replication competent recombinant retrovirus (see Fig. 2A of the patent), which is identical to the recombinant retrovirus of the instant application as recited in claims 66, 80, and 81 (compare Fig. 2A of the instant application with Fig. 2A of the patent). With respect to the limitations recited in claims 67-73, 75, 77-79, they are anticipated by the patented claims 2-17. Thus, the patented claims 1-18 and 21 anticipate claims 66-73, 75, 77-79 of the instant application. Since US Patent No. 6,258,789 B1 claim 1-18 and 21 embrace all limitation of the instant claims, the patent claims and the application claims are obvious variants of one another.

Claim 82 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 19 of U.S. Patent No. 6,899, 871. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

The instant claims claim 82 is drawn to a method of treating a subject having a proliferative disorder comprising contacting the subject with (i) a therapeutically effective amount of a recombinant replication competent retrovirus comprising a polynucleotide sequence encoding a GAG protein, a polynucleotide sequence encoding a POL protein, a polynucleotide sequence encoding a chimeric env protein comprising a targeting ligand, an oncoretroviral polynucleotide sequence comprising LTR sequences at the 5' and 3' end of the oncoretroviral polynucleotide sequence, wherein a tissue-specific

promoter sequence is contained within the U3 region of the LTR sequences at the 5' or 3' or 5' and 3' end of the oncoretroviral polynucleotide sequence, a heterologous nucleic acid sequence operably linked to a regulatory nucleic acid sequence, wherein the heterologous nucleic acid sequence encodes a suicide gene, and cis-acting nucleic acid sequences involved in reverse transcription, packaging and integration in a target cell, and (ii) a prodrug that is activated by the expression of the suicide gene.

The patented claim 19 recites a method of treating a subject having a cell proliferation disorder comprising: contacting the subject with a (i) therapeutically effective amount of a replication competent retrovirus comprising a nucleic acid sequence encoding a retroviral GAG protein, a nucleic acid sequence encoding a POL protein, a nucleic acid sequence encoding a chimeric retroviral envelope protein comprising a targeting ligand, an oncoretroviral polynucleotide sequence comprising LTR sequences at the 5' and 3' of the retroviral genome, wherein a tissue-specific promoter sequenced is contained within the LTR sequences at the 5' or 3' or 5'and 3'end of the oncoretroviral polynucleotide sequence, wherein the tissue-specific promoter sequence comprises at least one ARE obtained from the probasin promoter, a cassette comprising an IRES operably linked to a heterologous nucleic acid sequence encoding a polypeptide that converts a nontoxic prodrug to a toxic drug, wherein the cassette is postioned 3' to the sequence encoding the retroviral envelope and 5' to the 3'LTR sequence and/or 3' to the sequence encoding the retroviral envelope, and cis-acting sequences for reverse transcription, packaging and integration into the genome, and (ii) a nontoxic prodrug that is converted to a toxic drug by the polypeptide.

The instant retrovirus and the patented replication competent retrovirus are identical, as exemplified by Fig. 2A of the instant application and Fig. 2A of the patent that both disclose a replication competent retrovirus comprising a cassette with an IRES operably linked to a nucleic acid sequence encoding a suicide gene.

Thus, the patented claim 19 anticipates claim 82 of the instant application. Since US Patent No. 6,258,789 B1 claim 18 embraces all limitation of the instant claims, the patent claims and the application claim are obvious variants of one another.

Claim Rejections - 35 USC § 112 - enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, and 77-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands,* 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided.

The Breadth of the Claims

The instant claims are drawn to a method of treating a subject having a cell proliferative disorder by contacting the subject with a therapeutically effective amount of a retrovirus comprising a heterologous nucleic acid sequence encoding for a suicide gene and with a prodrug that is activated by the expression of the suicide gene.

The aspects considered broad are: (i) the range of proliferative disorders to be treated, and (ii) the range of retroviruses used to treat the proliferative disorders.

When read in light of the specification, the breadth of the claimed restroviruses clearly embraces any known retrovirus including those of foamy viruses such as HFV, lentivurses such as HIV-I, HIV-2 and SIV, MPMV viruses and MOMLV viruses.

The broad term proliferative disorder is not limited in any way by the specification, and in fact encompasses distinct diseases that are caused by different genetic factors and result in different clinical manifestation. For example, the term embraces neuronal disorders, such as Alzheimer's disease and Parkinson's disease, disorders associated with an overgrowth of connective tissue, such as various fibrotic conditions, including scleroderma, arthritis and cirrhosis, and neoplastic disorders.

As such, the as-filed specification attempt to claim that the disclosed replication competent retrovirus, as listed above, wherein a suicide gene is contained, can be

employed as a master drug to treat any cell proliferative disorder.

As will be shown below, these broad aspects are not enabled.

The Nature of the Invention

The nature of the invention is a method of treating proliferative disorders by using a suicide gene/prodrug system, wherein the suicide gene is delivered to the proliferating cells via a replication competent retrovirus.

The nature of such invention is within the broad genera of gene therapy for proliferative disorders and gene therapy for proliferative disorders does not generally enable Applicants' invention due to problems with the complexity and unpredictability of such disorders and, also due to problems with using nucleic acid-based therapies.

Susceptibility and outcome in complex proliferative disorders such as cancer are determined, at least in part by genetic polymorphism, and considerable difficulties remain in elucidating how many genes determine a particular phenotype. The etiology of cancer is multifactorial, and it is likely to involve the actions of genes at multiple levels along the multistage carcinogenesis process. How will therapeutic apply in these cases? For example, Carbone et al. (Seminars in Cancer Biology, 2004, 14: 399-405) teach:

> "In the past 40 years, there have been great advances in our understanding of cancer at the cellular and molecular level. However, this information has been difficult to translate to the bedside, and there has been little improvement in our ability to treat advanced solid tumors, i.e, carcinomas, the most common types of human cancers. The prognosis of metastatic carcinoma of the lung, larynx, breast, prostate, pancreas, liver, etc., has not significantly changed during the past 40 years. This is partly due to the fact that advanced solid tumors are genetically heterogeneous both among cases and within the same patient. They are also genetically instable (i.e., they continuously develop new genetic clones). Therefore, any new therapeutic agent identified is aiming at a "moving target" which can readily adapt to most forms of therapeutic attack."

Given these teachings, how would one of skill in the art know that any prodrug could be used to treat cell proliferative disorders without these cells developing drug resistance? Luqami YA teaches (Med Princ Pract, 2005, 14 Suppl 1: 35-48, Abstract):

> "Development of chemoresistance is a persistent problem during the treatment of local and disseminating disease. A plethora of cytotoxic drugs that selectively, but not exclusively, target active proliferating cells include diverse groups as DNA alkylating agents, antimetabolites, intercalating agents and mitotic inhibitors. Resistance constitutes a lack of response to drug-induced tumor growth inhibition; it may be inherent in a subpopulation of heterogeneous cancer cells or be acquired as a cellular response to drug exposure."

Therefore, the Artisan would not know what agent to use to treat a disease that can be caused by mutations in a number of different genes. Moreover, a polygenic disease such as cancer may require more than one pharmacological agent for treatment. How will therapeutic apply to polygenic diseases? The use of single agents may often not work very well, due to the complexity of regulatory pathways. Borisy et al. (Proc Natl Acad Sci USA, 2003, 100: 7977-7982) teach:

> "[p]atients with infectious diseases and with cancer have benefited from combination chemotherapy, where combinations of drugs are in many cases the standard of care".

Reviewing current strategies available for gene therapy in cancer, including suicide gene/prodrug systems, El-Aneed et al. (European Journal of Pharmacology, 2004, 498: 1-8) teach:

> "Due to the complex nature of cancer, cancer gene therapy includes many therapeutic strategies.
>
> It is expected, however, that successful cancer treatments will combine traditional therapies such as surgery, chemotherapy, and/or radiotherapy along with single or multiple gene treatments. The ultimate goal of these treatments is to eradicate cancer via various methods and effective therapies."

Applicants contemplate to use replication competent retrovirus comprising a suicide gene to treat any cell proliferative disorder. The use of retroviral vectors is known in the art to be unpredictable with respect to their capacity to deliver the therapeutic gene to all tumor cells, as evidenced by El-Aneed (Journal of Controlled Release, 2004, 94, 1-14), who teaches:

> "Most of the retroviruses, however, infect actively dividing cells during mitosis. Despite the fact that this feature might protect the normal tissues and provide natural targeting to the tumor, all tumors contain non-dividing cells in the resting G_0. Such cells can escape therapy. Lentiviruses such as human immunodeficiency virus (HIV) and their vectors can, however, infect non-proliferating cells."

Even if lentiviral vectors are used, the problems with using nucleic acid-based therapies still need to be overcome. For example, Meyer et al. (Review, Cell. Mol. Biol., 2001, 47: 1277-1294) teach:

> "Although gene therapy provides the hope and potential to revolutionize the future of medicine, this optimism must be tempered. Ongoing efforts to both quantitatively increase both gene transfer and expression to achieve improved therapeutic effect and to restrict the distribution and expression to relevant target tissues are under development. This includes enhancing the permeation of the vectors, development of targeted vectors that can be delivered systematically and regulating the level and target cell specificity of gene expression. Although these technologies are under development, advances in these areas will further improve the efficacy and safety of gene therapy vectors and further increase chances of success."

Hence, from the nature of the invention, the Artisan would not reasonably predict that the retroviral vector claimed by the instant application could be used to treat proliferative disorders in general.

The State of the Prior Art and the Level of Predictability in the Art

Applicants contemplate to use a two-step treatment for cell proliferative disorders, consisting of delivery of a suicide gene, followed by the administration of a

prodrug that is activated by the expression of the suicide gene in the targeted cells to treat any cell proliferative disorder, i.e., gene directed enzyme prodrug therapy. However, at the time the invention was made, and even in the present, the art of using viral directed enzyme prodrug therapy for proliferative disorders was known to be unpredictable. With respect to gene-directed enzyme prodrug therapy (GDEPT), Springer et al. (J Clin Invest, 2000, 105: 1161-1167) teach:

> "Effective tumor destruction with GDEPT depends on the design of the gene-therapy vectors, the chemistry of the prodrugs and their toxic metabolites, and the means to deliver one or both components specifically to the target cells. Vectors, the vehicles in which the transgenes reach the tumor cell, must be careful tailored to specific GDEP systems. The specificity of targeting to cancer cells and efficient transfection are essential for effective GDEPT, as are the toxicity of the vector and the uptake of prodrugs or drugs by normal and malignant cells.
>
> Some hurdles must be overcome before GDEPT will become a clinically efficient treatment for cancer. Major improvements are needed in vector design to enhance targeting and delivery of suicide genes.

Applicants envisage the use of replication competent retroviruses to deliver the suicide genes to the targeted cells/tissues. The problems of retroviral vectors based therapies are well known in the art, particularly with regard to the delivery, the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is expressed to a degree necessary to result in a therapeutic effect.

With respect to the problems encountered with the delivery, Gardlik et al. (Review, Med. Sci. Monit., 2005, 11: RA110-121) teach:

> "The simplest way of gene delivery is injecting naked DNA encoding the therapeutic protein, but because of low efficiency there is a need to use special molecules and methods to improve gene delivery.
>
> Two kinds of vectors have been employed as vehicles for gene transfer. Viral vectors for gene transduction, such as retroviral, adenoviral, and adeno-associated viral vectors, and non-viral vectors for gene transfection, such as plasmids and liposomes. However,

> each vector has its own advantages and disadvantages: none of these types of vectors has been found to be ideal for both safe and efficient gene transfer and stable and sufficient gene expression"

Assuming that the delivery problems can be solved, an additional barrier towards successful gene therapy is presented by gene silencing that results in loss of expression of the therapeutic gene. Thus, in his review, Bestor (J. Clin. Invest., 2000, 105: 409-411) teaches :

> "Gene therapy usually depends on a construct or recombinant virus that directs the expression of an agent (protein or RNA) in a particular tissue. Delivery to the target tissue has long been recognized as a difficult problem, as has proper cell type-specific regulation. The existence of gene silencing, the recognition and inactivation of alien genes by target cells, has only been recently recognized as an additional challenge to gene therapy. Many cases are known in which a transferred gene undergoes a brief period of expression followed by a decline to undetectable levels without the loss of the expression construct.
>
> [I]t is now clear that mammalian genes can be inactivated or silent, even in the presence of all factors normally sufficient for their expression, and that cells can detect alterations of their genomes and respond by imposing a strong and heritable silencing effect.
>
> [G]ene silencing has already compromised a number of gene transfer efforts and it is likely to represent a barrier to many of the forms of gene therapy currently under development. Even if the delivery and regulation problems can be solved, it is not unlikely that successful gene transfer and tissue-specific expression may be followed by dwindling expression and loss of therapeutic effect unless silencing-resistant expression constructs are developed and used."

To achieve better efficacy Applicants rely on the use of a tissue specific promoter to restrict transcription specifically to tumor cells. However, the state of the art with respect to the use of a tissue specific promoter to controlled gene expression remains an experimental stage at best. Problems with using vectors for tissue specific replication include interference of vector sequences with regulatory sequences, particularly where the vector is derived from a virus, interference from sequences after

vector integration, i.e., positional effects, non specific effects on host transcription (Miller et al., Human Gene Therapy, 1997, 8: 803-815). Along these lines, Vassaux et al. (Expert Opin Biol Ther, 2004, 4: 519-530) teach that expression from the tissue specific promoter might be inhibited by the viral promoter, phenomenon known as promoter interference (p. 524, column 1, last paragraph) and Vile et al. (Molecular Medicine Today, 1998 4: 84-92) teach:

> "the relevant locus control regions/enhancer/silencer/promoter sequences that control expression can be distributed over many kbp and within chromatin domains that are difficult to reproduce within the context of the vector systems", and that "the combinations of these elements in certain configurations of these elements in certain configurations might be successful in the context of one vector (such as plasmid DNA), but their specificity might be altered or lost in a different context (such as retrovirus or adenovirus)".

Even if assuming for argument, that a tissue specific promoter driven retroviral vector is targeted to a desired tissue; transient gene expression which is not correlative to a therapeutic effect remains an important issue that needs to be resolved. Anderson (Nature, 1998, 392: 25-30) teaches:

> "Another potential problem results from the ability of retroviral vectors to integrate randomly into host cell DNA. For example, a vector might insert itself into a tumour suppressor gene, thereby increasing the propensity of the cell to become cancerous. The only example of unintentional tumour production in a retroviral gene transfer experiment in large animals was published in 1992., three cases of lymphoma were reported among ten rhesus monkeys whose bone marrow had been destroyed by irradiation and who were then transplanted with haematopoietic stems cells that had been exposed to a large number of RCR as well as the experimental vector.
>
> Except for anecdotal reports of individuals patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease".

Applicant's claims encompass the use of a generic RCR vector, an enormous number of cell proliferative disease sites, and routes of administration other than direct

administration. Clearly, the Anderson reference alone does indicate that even short-term gene expression or transient gene expression is not equivalent to a therapeutically relevant effect, and that routes of administration and/or types of vectors used as carrier for therapeutic DNA are crucial for a successful treatment effect.

To further support the complexities and the unpredictable nature of therapeutic applications of gene therapy vectors, and to further support that the presence of gene therapy clinical trials is not the same as an indicia of the a reasonable predictability of gene therapy, Romano (Stem Cells, 2000: 18, 19-39) teaches:

> "Over the last decade, more than 300 phase I and phase II gene-based clinical trials have been conducted worldwide for the treatment of cancer and monogenic disorders....The aim of these clinical trials was mainly to assess the degree of toxicity of the various gene delivery systems and the constructs employed in the study. The possible therapeutic efficacy of the clinical trials was only a secondary issue, which in many cases could not even be determined because of the preliminary nature of the study design.

Regarding the issue of using tissue specific retroviral vectors in gene therapy application, Romano teaches:

> "Overall, the in vivo administration of retroviral vectors poses a number of additional safety concerns and technical limitations if compared to the ex vivo gene transfer models. To pursue the goal of safe and efficient in vivo retroviral transduction, it is necessary to generate tissue or cell specific retroviral vectors, which can integrate safe cell chromosomal sites. The latter issue has never been tackled, whereas the engineering of ecotropic-based retroviral vectors with altered cell tropism has attracted much attention, but all the attempts had little success. The chimeric retroviral particles that have been produced have a low transduction capacity, or even fail the gene transfer process".

Meng et al. (Gene Therapy of Cancer, Chapter 1, 1999, pp. 3-20) teach that factors including specific genes used for a treatment, gene delivery vectors, routes of administration, and gene expression are all critical for the success of a gene therapy

method (p. 4-6). For example, Meng et al teach that "it is difficult to prepare sufficiently high titers of retroviruses for in vivo gene therapy", and that "although it may seem intuitive that a heightened immune response may be good in cancer gene therapy, it is less desirable on a practical scale because the immune response helps to eliminate the vector and to decrease the expression of the transduced gene" (p. 4, column 2, last paragraph). Meng et al. further teach that "although animal studies have suggested low toxicity and excellent efficacy, these investigations have been limited by the use of immuno-deficient mice" (p. 6, column 1).

With respect to administration routes, Meng et al. teach that other than intratumor injection, delivery of virally expressed genes by intravascular or intracavitary injections also presents barriers to the delivery of the target genes (p. 6, column 1). For example, Meng et al. state:

> "In intravascular administration, instillation into a peripheral vein dilutes the vehicle, so only a small portion may ultimately reach the tumor. Intravascular administration also elicits a powerful immune response. Tropism for organs such as the liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous if the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass. In the case of intracavitary administration (i.e., intrapleural or intraperitoneal), the surface of the tumor mass is coated by virus, but intratumoral delivery within a solid mass represents an important barrier"

With respect to the embodiments drawn to non-neoplastic cell proliferative disorders, e.g., gene therapy for inherited neurological diseases, Martin (TIBTECH, 1995, 13: 28-35) teaches (p. 29, column 2), that "it is apparent that the development of a therapeutic strategy for inherited neurological diseases will require a spectrum of approaches, and it is unlikely that gene replacement will emerge as a successful

treatment in the near future for disorders that affect mature neurons in the CNS (central nervous system)", and that "the difficulties that are inherent in transferring genes to postmitotic, nonregenerative cells in the CNS are all too clear". Martin further concludes on page 35 that "it is apparent that approaches to the treatment of neurological disorders using the new techniques of molecular biology, to date, promised more than they have delivered", and that "the problems of delivery of genes via vectors to postmitotic neurons will remain a serious limitation in gene therapy". Regarding the unpredictability of gene delivery routes and target sites using gene therapy for disorders affecting the central nervous system (CNS), Zlokovic et al. (Neurosurgery, 1997, 40: 805-813) state that "a major obstacle to gene therapy for disorders affecting the CNS, either locally or globally, is the delivery of genetic material to the brain because of the present of the continuous tight-junctioned cerebral capillary endothelium comprising the BBB (blood brain barrier)" (p. 807 bridging p. 808), and that "unless there is a specialized transport system that requires interaction with a specialized transporter and/or receptor at the BBB, large biological particles,including genetic vectors, are normally rejected by the BBB" (p. 809, column 1). Zlokovic et al. further concludes on page 81 1, column 1, that technical issues for the success of gene therapy in the treatment of CNS including (i) transfection efficiency, (ii) delivery of genetic material across vascular barriers of the CNS and brain tumors, and (iii) control of expression of the transgene only in target CNS cells remain a challenge at the time the invention was made.

These problems still need to be overcome, as evidenced by Lowenstein et al.

(Review, Current Opinion in Pharmacology, 2004, 4: 91-97) who teach:

> "Could vectors, transgenes or transgenic proteins access the brain from the circulation? Delivery of viral vectors into the brain through a systemic route would be of great importance, but has so far neither been achieved nor explored in detail. Clearly this would be attractive because of the large areas of the brain that are affected in human neurodegenerative diseases."

In his review article, Tuszynski (Gene Therapy, 2003, 3: 815-828) states:

> "[t]here are also some relative potential disadvantages of *in vivo* gene therapy, including: non-specificty of target cell infection - many different cell types can be infected when *in vivo* vectors are injected into CNS, including neurons, glia and vascular cells.
>
> Thus, the potential of gene therapy to treat disease of the nervous system is vast and unprecedented, yet entirely hypothetical at this early stage of development."

In view of the reasons set forth above and of numerous issues, as indicated above, which need to be overcome in order to achieve the broadly claimed objective of the claimed subject matter, a skilled artisan would reasonably conclude that the state of the art of suicide gene therapy by employing tissue specific replication competent retroviruses to treat any cell proliferative disorder, remains reasonably unpredictable at the time of filing. Vassuax et al. teach:

> "It appears that suicide gene therapy has not been selected by the industry as a worthwhile strategy to develop gene therapy products. Many reasons can explain this and many improvements are required before GDEPT can become a successful therapy."

The Amount of Direction or Guidance/The Existence of Working Examples

Given the breadth of the claimed invention, and the complexities associated with the nature of the claimed invention, one skilled in the art would have to turn to the specification for guidance. However, as indicated above, and even assuming that the level of one skilled in the art is relatively high in the prior art, the guidance provided by

the specification is not sufficient to overcome the doubts and obstacles expressed in the art of record. As such, the only issue left is the working examples provided by the specification.

Example 1 provides in vitro results showing a reporter gene expression in cultured cells.

Example 2 provides a protocol wherein a reporter gene encoded retrovirus is intratumorally injected in nu/nu/ BALB/C mice, however, no statistical results can be used to correlate to an anti-cancer effect.

Example 3 provides a protocol for a creation of RCR vector producing cell line. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Examples 4-6 provides a prophetic protocol for testing tissue specificity of a marker gene encoded RCR. No results are shown. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 7 shows that a RCR having a probasin promoter being incorporated into the retrovirus LTR was able to drive expression of a reporter gene in cultured cells. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 8 provides a prophetic protocol in an attempt to show transduction of prostate tumors in a transgenic mouse model. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 9 shows expression of a reporter gene in breast cancer cells after an

intratumoral injection of an MoMLV RCR encoding a GFP gene. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 10 provides protocols for utilizing IRES sequences in RCR, and shows that the RCR was able to transduce cultured cell. No data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

Example 11 provides a prophetic protocol showing how to make RCR vectors targeted to breast tumor cells using two types of modification to the Env protein. However, no data showing any therapeutically relevant effect in the treatment of a cell proliferative disorder are present.

These examples do not appear to reasonably render the claimed invention as a whole patentable under 35 USC, 112, first paragraph, particularly given the doubts expressed by numerous cited art, as indicated above. The totality of the prior art appear to teach that at the time of filing while transient gene expression has been observed in cells in vivo at the time of filing using routes of administration other than intratumoral administration, it is not apparent how a randomly transient gene expression in a tumor bearing animal wherein a nude mouse with an intratumoral injection of a marker gene expressing retroviral vector (RCR) is reasonably correlated to a successful targeted cancer gene therapy wherein a replication competent retrovirus is employed or to any meaningful or sufficient amounts of the claimed viral vectors inside only target cancer cells so as to produce only targeted killing effects in the cancer cells. Fillat et al. (Curr Gene Ther, 2003, 3: 13-26) teach:

"Many of the different strategies designed so far have been first tested *in vitro* in cellular models followed by pre-clinical studies in mouse and rat models. The validation of the different approaches in animal models has been the clue to move forward and enter into the clinical application. However, poor results have been obtained so far from the clinical trials undertaken. The reasons for the apparent lack of efficacy of HDVtk-based strategies are many and concern the gene therapy itself. First, evidence of extensive tumor cell transduction after intratumnoral or intracavitary injection of viral vectors is lacking. Currently available vectors might simply be ineffective in delivering therapeutic transgenes to human tumors. In fact, no single gene therapy trial has conclusively shown an antitumor effect of a gene therapy product given alone. It was hypothesized that the bystander effect observed after genetic prodrug activation in a variety of animal models of neoplastic disease might obviate the need of extensive tumor transduction. But in the case of HSVtk, such bystander effect depends on the production of large amounts of enzyme in the transduced cells that might in turn result in a significant amount of ganciclovir being transferred to the neighboring cells. However, this may probably not happen in humans either due to immune destruction of transduced cells or to transgene silencing. Moreover, for tumors to regress after HSVtk production, ganciclovir has to reach neoplastic cells and it is established that impaired delivery contributes to drug resistance in many human tumors."

As such, the specification fails to teach one of skill in the art how to overcome the unpredictability of vector targeting such that efficient gene transfer is achieved by a generic heterologous nucleic acid, a generic retrovirus vector and a generic route of delivery of a retrovirus construct as claimed for the treatment of a number of proliferative cell related diseases as contemplated by the as-filed application.

Conclusion

Thus, the specification is not enabling for the broad claims of treating a subject having a cell proliferative disorder by contacting the subject with a therapeutically effective amount of a retrovirus comprising a heterologous nucleic acid sequence encoding for a suicide gene and with a prodrug that is activated by the expression of the suicide gene, as the art of genedirected enzyme prodrug therapy is neither routine nor predictable. While the intent is not to say that suicide gene/prodrug systems utilizing retroviral vectors to deliver the suicide genes can never be used to treat cell proliferative

disorders, the intent is to provide art taught reasoning as to why the instant claims are not enabled.

In order to practice the claimed invention *in vivo* in all organisms a number of variables would have to be optimized, including: (i) the mode of delivery of retroviral vectors to an organism that would allow it to reach the targeted cell, (ii) the amount of retroviral vector that would need to be delivered in order to express a stable and sufficient amount of the therapeutic gene for prevention or treatment, once it reached the proper cell, (iii) ensuring that the nucleic acid remains viable in a cell for a period of time that allows expression to an extent that there is a measurable and significant therapeutic effect, and (iv) overcoming drug resistance. Each one of these variables would have to be empirically determined for each suicide gene/prodrug system. Optimization of any single one of these steps is not routine, and, when taken together, the amount of experimentation required becomes such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue, trial and error experimentation and therefore, claims 41-45, 49-51, 56, 58, 59, 61, 63-73, 75, and 77-82 are not enabled.

4. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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